Role of spinal LPCAT2, an inducible PAF synthesis enzyme on development and maintenance of painful peripheral neuropathy models in mice

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Pain in peripheral neuropathies is produced by damage or illness affecting nerve fibers themselves, and often resistant to current analgesics. We have previously suggested that PAF may be a mediator of neuropathic pain. PAF injection into the mouse spinal cord caused thermal hyperalgesia and tactile allodynia, which were at least in part mediated by spinal dysfunction of glycine receptor $\alpha 3$ (GlyRa3) and were blocked by PAF receptor antagonists [Morita et al., Pain 111:351-359,2004; Pain 138: 525-536,2008]. Subsequent studies showed PAF receptor blockade reduced pain behaviors elicited in nerve injury models [Okubo et al., Mol Pain 8(8):doi:10.1186,2012; Motoyama et al., Eur J Pain 17(8):1156-1167,2013; Morita et al., PlosOne 9(3):e91746,2014].

The present study examined the pain relieving effect of knockdown of spinal LPCAT2, a novel inducible PAF synthesis enzyme, and of specific inhibitor of LPCAT2 (TSI-01) on several neuropathic pain models (partial sciatic nerve ligation-injury model, painful diabetic neuropathy model, bone cancer pain model, chemotherapeutic agents-induced painful neuropathy, chronic and acute inflammatory pain models in animal).

This study demonstrated that the amount of a LPCAT2 protein significantly increased in the spinal cord after sciatic nerve ligation and transplantation of NCTC 2472 tumor cells into mouse tibia [Morita et al., PlosOne 9(3):e91746,2014]. The knockdown of spinal LPCAT2 and PAF receptor by intrathecal small interfering RNA (siRNA) transfer 15 days after sciatic nerve injury ameliorated tactile allodynia. Knockdown of LPCAT2 and PAF receptor 3 day before sciatic nerve injury prevented the development of pain until 130 days after surgery. Single administration of TSI-01 and repeated administration of specific PAF receptor antagonist (TCV-309) abolished the appearance of pain behaviors at pre- and post-surgery in the partial sciatic nerve ligation injury model, respectively. The anti-nociceptive effects of knockdown of LPCAT2 and PAF receptor, repeated administration of PAF antagonist TCV-309 and LPCAT2 inhibitor TSI-01 was appeared certainly in any other models tested.

These data suggest that spinal LPCAT2 play a causal role in the development and maintenance of neuropathic pain in animal models, and that LPCAT2 antagonists may highlight a potential novel therapeutic strategy for the treatment of persistent neuropathic pain.